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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/720,006	KARL ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/15/07, 7/27/07, and 1/2/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-48,73 and 75-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-48,73 and 75-80* is/are rejected.

7)☒ Claim(s) *44,45,75 and 77* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/15/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/15/07 and the supplemental Reply of 7/27/07 have been entered.

2. Applicant's response to the Requirement for Information under § 1.105, filed 1/2/08, is further acknowledged. The Requirement related to the equation for calculating a cut-off index (COI) disclosed in the specification on page 22 and characterized therein as "conventional". Applicant submits that although the concept of calculating a COI is conventional, the particular formula shown on page 22 is new (see the Reply of 1/2/08, page 2). Applicant also submits that information about similar calculations is not readily available but that U.S. 6,815,217 discloses another calculation of a cut-off index and that different calculations such as COI = (signal $_{\text{test field}}$ = Signal $_{\text{negative control field}}$)/3 x Signal $_{\text{negative control}}$ and COI = signal $_{\text{sample}}$/signal $_{\text{negative sample}}$ have been described in the art (Reply, pages 3-4). Applicant's response is acceptable and the Examiner thanks Applicant for clarifying the record.

3. Claims 44-45, 47-48, and 73 were amended. Claims 49-52 and 74 were canceled. New claims 75-80 were added. Accordingly, claims 44-48, 73, and 75-80 are currently pending and subject to examination below.

Objections/Rejections Withdrawn

4. The objection to claim 44 has been obviated by the amendments.

5. The rejections of claims 49-52 and 74 are moot in light of the claims' cancellation.

6. The rejections of claims 48 and 51-52 under § 112, 1st paragraph as containing new matter set forth in the previous Office action (see the Office action mailed 2/15/07 pages 7-8, item 15) have been withdrawn in response to Applicant's amendments to recite that the third receptor binds specifically with the *analyte*.

7. The rejections under § 112, 2nd paragraph not reiterated below have been withdrawn.

8. The rejections of claims 44, 47-48, and 73 under § 102(b) as being anticipated by Herzberg et al. are withdrawn in light of the amendments to claim 44 to recite calculation of a cut-off index..

9. The rejections of claims 44-46, 48, and 73 under § 103(a) as being unpatentable over Ekins in view of Schonbrunner and Lancaster, and of claims 47 and 74 under § 103(a) as being unpatentable over the noted references in view of O'Connor, have been withdrawn in light of the amendments to claim 44.

Information Disclosure Statement

10. The information disclosure statement filed **6/15/07** has been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached form PTO-1449.

11. Cite Nos. 2-5, 7, and 9 have been lined through to avoid duplicate citation as the references indicated are already of record. Specifically, US 5,126,276 and US 5,432,099 were

cited by the Examiner in the Office action mailed 12/3/02; US 5,627,026 was cited on Applicant's IDS of 5/21/01 and considered by the Examiner as indicated by the signed copy attached to the Office action of 12/3/02; US 5,516,635 was cited by the Examiner in the Office action mailed 5/30/06; WO 97/32212 was cited by the Examiner in the Office action mailed 12/3/02; and EP 0 171 150 A2 was cited by the Examiner in the Office action mailed 2/15/07.

Claim Objections

12. Claims 44-45, 75, and 77 are objected to because of the following informalities:

13. Claim 44 recites that a COI "is indicative for presence" of a specific analyte, which is grammatically awkward. The language --is indicative of the presence-- is suggested for clarity.

14. Claim 44 recites "a specific analyte" in the last two lines of the claim. It appears that this refers to one of the plurality of analytes earlier recited, but this is not made clear. Clarification is requested as to the relationship of the "specific analyte" to the "plurality of analytes derived from one pathogen".

15. Claim 45 recites a Markush-type group: "selected from the group consisting of HIV I, HIV II, HBV, and HCV-antibodies and HIV antigens". The use of two terminating "ands" is confusing. Clarification is needed.

16. Claim 44 recites a "signal generating group" while claim 48 employs the hyphenated "signal-generating group". Applicant is requested to employ consistent terminology.

17. Claim 44 refers to a "plurality of analytes derived from one pathogen" in the preamble; to "analyte-specific" receptors" and to "different analytes" in part (a). Applicant is requested to clarify the relationship of these various analytes to each other. In particular, it would seem that

the receptors are specific for the analytes to be detected, and that the "different analytes" refers to different analytes among the plurality of analytes to be detected. However, the claim does not make this clear.

18. Regarding claims 45, 75, and 77, it is suggested that in the first instance of the abbreviations HIV, HBV, and HCV in the claims that these be accompanied by the full terms.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

19. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claims 44-48, 73, and 75-80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 44, as instantly amended, recites the step of

> calculating a test area-specific cut-of index (COI) on each test area, wherein a COI larger than 1 for one test area is indicative for presence of a specific analyte in the sample.

There is no generic disclosure that <u>any</u> calculated COI greater than 1 would indicate a positive result as now claimed. The specification does disclose a specific example in which a COI of greater than 1 was used to indicate a positive result: see page 30, bottom, equation

designated by two asterisks. However, this is disclosed in the context of a specific COI calculated using a specific equation. A very similar COI, calculated in a similar manner but using a different value of *n*, is disclosed as signaling the exact opposite (a negative result) when the value of the COI is greater than 1. See page 30, equation designated by the single asterisk.

Therefore, one skilled in the art would not understand the disclosure of a specific COI greater than 1 being indicative of a positive result to apply universally to any COI, since COIs calculated by other means could signal the opposite. Furthermore, since COI calculations could be made using different equations, having different variables and different mathematical operators, one skilled in the art would recognize that for a given analyte the threshold for a positive assay would differ depending on how the COI is calculated.

For example, taking the case of the equation recited in claim 78, assume that the value of *n* is 3 and that a COI greater than 1 signals a positive assay. However, if the value of *n* is instead set to be 1, the resulting COI would be reduced by a factor of 3. If one analyzed the results of the same assay on the same analyte using the latter equation instead of the former, a COI greater than 3 (rather than greater than 1) would signify a positive assay. For these reasons, the disclosure of a COI of greater than 1 signifying a positive result is only meaningful in the context of the specific calculation and the specific assay in which it was disclosed.

In addition, the disclosure of the COI on page 30 was also in the context of a specific assay, namely an assay for HIV-1 p24 antigen. However, the claims are not limited to methods in which the analyte is p24. Furthermore, as recited in the claim the COI being calculated is specific to a particular test area. This concept of the threshold or cut-off value being specific to the test area, i.e. to the analyte being detected, is also conveyed at page 11, last full paragraph and on

pages 21-22 ("The use of predetermined test-area-specific threshold values for each individual test area..."). In other words, different threshold values would be set for different analytes. As such, one skilled in the art would not understand the COI of 1, disclosed in the context of p24, to be universally applicable to any analyte as now claimed.

Since the instant claims are not limited in the manner by which COI is calculated, the incorporation of the limitation "wherein a COI larger than 1 for one test area is indicative for presence of a specific analyte in the sample" out of the context of the equation and assay in which it was originally disclosed represents new matter, as it introduces a new subgenus.

Disclosure of a genus and species of subgenus within that genus is not sufficient description of subgenus to satisfy description requirement of 35 U.S.C. 112, unless there are specific facts that lead to determination that subgenus is implicitly described. Ex parte Westphal, 26 USPQ2d (BPAI 1993). In re Smith 173 USPQ 679 (CCPA 1972). Although the specification discloses generally that a COI may be calculated, and further that certain COI calculations for certain analytes may signify a positive result when the COI is greater than 1, there is no disclosure that any calculated COI greater than 1 would indicate a positive result as now claimed. For these reasons, the amendments broaden the scope of the original disclosure in a manner not supported by the specification and claims as filed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

21. Claims 44-48, 73, and 75-80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

22. Claim 44 recites a plurality of analytes "derived from" one pathogen. This terminology renders the claim indefinite because the specification does not define the term "derived from" in this context. Although antigens that are HIV proteins are disclosed, as well as antibodies specific for such proteins, it is unclear what other analytes or types of analytes would also be considered to be "derived from" a pathogen. It is unclear by what process or processes the analytes would be "derived". For these reasons, the metes and bounds of the claim are unclear. Would this encompass, for example, antigens from different viruses that evolved from a common precursor? Analytes generated through recombinant engineering of known bacterial proteins whose sequences are altered via mutagenesis or other means?

23. Claim 44 recites the limitation "the test area" in line 3 of part (b). There is insufficient antecedent basis for this limitation in the claim because the claim previously recites both a "first test area" and a "second test area". Therefore, there is ambiguity as to which test area is meant.

24. Claim 44 recites the limitation "the signal generating group bound to the first and second test areas" in lines 2-3 of part (c). There is insufficient antecedent basis for this limitation in the claim because although the claim refers to "a signal generating group" in part (b), there is no prior mention that this group is bound to the first and second test areas.

25. Claim 44 recites the limitation "the analytes bound to the test area" in lines 2-3 of part (b). There is insufficient antecedent basis for this limitation in the claim because there is no prior mention that the analytes are bound to the test area.

Furthermore, the preamble recites a "plurality of analytes derived from one pathogen", while part (a) of the claim refers to "analyte specific" receptors and also to "different analytes". There is no requirement that these analytes be one and the same. Therefore, the recitation of "the analytes" is ambiguous because it is not apparent which analytes are being invoked.

In addition, if "the analytes" is referring back to the "different analytes" to which the first and second receptors bind, it is unclear why each different analyte would bind to "the" test area, since each test area has a receptor specific for a different analyte. It is unclear how a receptor specific for one analyte could be used to bind an entirely different analyte as implied by "the analytes bound to the test area".

26. Claim 44 is indefinite in reciting "a test-area-specific cut-off index (COI)...wherein a COI larger than 1 for one test area is indicative for presence of a specific analyte in the sample". This reference to a specific index value being larger than 1, absent a definition or indication of what the index value is or how it is calculated, and absent a recitation of scientific units that would characterize the numerical value given, renders the claim indefinite.

Furthermore, the claim is also indefinite because it refers to an object that is variable. See MPEP 2173.05(a). In particular, as made clear by dependent claims 78-80, the value of the COI may vary depending on the value of n in the example of the COI equation of claim 78. Since the COI depends on parameters which may vary, one skilled in the art would not be able to determine the metes and bounds of the claim.

27. Claim 44 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a step in which a plurality of analytes is detected.

The objective of the method, as recited in the preamble, is to detect a plurality of antigens. However, the claim concludes with step (d) in which a test area-specific COI is calculated. The claim indicates that a COI larger than 1 is indicative for the presence of "a specific analyte". However, this step cannot be clearly correlated with detection of a plurality of analytes. For example, the conclusion step refers only to "a specific analyte" rather than to a plurality of analytes. Furthermore, there is no recited connection between the "specific analyte" and the plurality of analytes earlier recited. Active method steps or alternatively, a correlation step should be included to describe how the results of the method accomplish the objective as recited in the preamble.

28. Claim 44 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: that the third receptors are specific for the analytes to be detected. The claim recites a detection agent comprising one or more third receptors "to allow binding of the third receptors to the analytes bound to the test area". However, it is unclear how the receptors would bind unless they were related to the analytes to be detected. In other words, it would seem that each of the third receptors must be capable of specific binding to one of the plurality of analytes.

29. Claim 48 recites that the detection reagent "comprises at least one third receptor". However, step (b) of independent claim 44 already recites that the detection reagent comprises one or more third receptors. It is unclear whether claim 48 is referring to the same one or more third receptors of claim 44, or alternatively, to a different third receptor. Similarly, claim 48 also

recites "a signal-generating group which is either directly bound to the third receptor or which is a universal detection reagent comprising labeled latex particles which binds to the third receptor". This is confusing since part (b) of claim 44 already recites that the detection reagent is directly or indirectly labeled with a signal generating group. If the elements in claim 48 are meant to refer back to those previously recited, this should be indicated by reciting, for example --the signal generating group-- or --said signal generating group--.

Claim Rejections - 35 USC § 102

30. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

31. Claims 44-45, 47-48, 73, and 76-79 are rejected under 35 U.S.C. 102(a) as being anticipated by Karl et al. (WO 99/05525, Applicant's Information Disclosure Statement of 6/15/07).

It is noted that while the reference is a German language document, an English translation is available by way of its U.S. counterpart, US 6,815,217 B2 (of record). The column and line numbers indicated below refer to the text of US 6,815,217 B2.

Karl et al. teach a method for detecting at least one analyte in a sample using a solid phase having at least one spatially discrete test area (abstract and column 1, line 66 to column 2, line 61; column 6, lines 56-64; and claim 17 in particular). The solid phase is preferably non-porous, e.g. plastic, glass, metal, or metal oxide (column 2, lines 29-32). In one embodiment, a

plurality of analytes derived from a single pathogen are assayed, namely HBs antigen and anti-HBc antibodies (which would be considered to be each "derived from" hepatitis B virus). Immobilized antibody specific for HBs antigen (i.e., first receptor) and immobilized HBc antigen (i.e., second receptor) are bound to discrete test areas on the solid support. See Figure 1 and column 2, lines 3-20, 34-39, and line 62 to column 3, line 14. The reference further teaches contacting the sample with the solid support and with a detection reagent, namely a specific binding reagent for the analyte having a suitable marker group, e.g. fluorescent marker group, and the detection reagent may be a "universal" marker group. See column 2, lines 39-64; column 3, line 17; claim 34, step (b) and Figure 1. The signals from the marker groups are separately measured for each test area (see column 6, lines 34-45 and the Tables presented in the Examples). This is also made clear for example in claim 19, where test and control areas are separately measured in steps (c) and (d), respectively.

Karl et al. further teach calculating a test area-specific cut-off index (COI). See column 5, line 66 to column 6, line 45, and in particular in the Tables presented in the examples. For the case of the analyte HBs antigen, Karl et al. teach that a COI greater than 1 indicates a positive test, i.e. the presence of the analyte (see column 8, lines 1-24).

With respect to claim 47, Karl et al. teach control areas for detecting false results caused by interferences (see, e.g., the abstract; column 1, lines 11-33; column 2, lines 21-28; column 3, line 30 to column 4, line 60; and column 10, lines 45-49).

With respect to claim 48, Karl et al. teach universal marker groups comprising fluorescent latex beads (column 2, lines 62-67 and Figure 1).

With respect to claims 78-79, Karl et al. teach calculating the COI by the formula COI = [Signal (test field) – signal (negative control field)]/3 x signal (negative control). See the Tables in the Examples, e.g. at column 8, lines 19-20. Absent a specific or limiting definition for the variables recited instantly, this equation reads on that currently recited even though slightly different terminology is used. Specifically, the "Signal (test field)" of Karl et al. denotes the signal measured in the test, i.e. sample area. Karl et al. indicate that the negative control field refers to unspecific binding in the control field without solid phase receptor (column 8, lines 17-18), such that "signal(negative control field)" would read on the instantly claimed "$background_{sample}$" since it denotes signal due to the nonspecific interaction of sample with the solid support, i.e. background. The value 3 would be considered "n" and the signal (negative control) would read on the instantly recited "$background_{negative\ control}$" since signal associated with a negative control would be considered "background" signal since it is not reflective of the presence of analyte.

Claim Rejections - 35 USC § 103

32. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

33. Claim 46 is rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Karl et al.

Karl et al. is as discussed above, which teaches that the test areas most preferably have a diameter of 10 microns (0.01 mm) to 2 mm (column 2, lines 9-10). Such a range largely overlaps the claimed range of 0.01 mm to 1 mm, such that the claimed range is anticipated with sufficient specificity in the absence of evidence of criticality for the narrower range. See MPEP 2131.03.

However, even if the range of 0.01 mm to 1 mm is held not to be anticipated with sufficient specificity by the prior art range of 0.01 mm to 2 mm, a *prima facie* case of obviousness also exists given that the claimed range largely overlaps the prior art range. See MPEP 2144.05. As such, it would have been obvious to one of ordinary skill in the art to arrive at the claimed range by selecting values within the prior art range out of the course of routine optimization. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

34. Claim 80 is rejected under 35 U.S.C. 103(a) as being unpatentable over Karl et al. in view of Ohkawa et al. ("Hepatitis C virus antibody and hepatitis C virus replication in chronic hepatitis B patients" J Hepatol. 1994 Oct;21(4):509-14), Ohnishi et al. ("Detection of anti-hepatitis C virus antibody in fulminant hepatic failure" Gastroenterol Jpn. 1991 Jul;26 Suppl 3:212-5), Hyman et al. (US 5,384,240), Chan et al. (US 5,120,662, of record), Lesniewski et al. (US 6,596,476 B1), Kiyosawa et al. ("Significance of IgM antibody to hepatitis B core antigen for the differential diagnosis of acute and chronic hepatitis B virus infection and for the evaluation of the inflammatory activity of type B chronic liver diseases" Gastroenterol Jpn. 1986 Dec;21(6):601-7), and Yuki et al. ("The significance of immunoglobulin M antibody response to

hepatitis C virus core protein in patients with chronic hepatitis C" Hepatology. 1995 Aug;22(2):402-6).

Karl et al. is as discussed above, which teaches the equation COI = [Signal (test field) – signal (negative control field)]/**3** x signal (negative control), where 3 corresponds to the instantly claimed "n". However, the reference fails to specifically teach using a value of 2 instead of a value of 3 in the above equation.

However, when taken together with the general knowledge in the art of clinical diagnostics, it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention by optimizing the equations disclosed in Karl et al. The following references are cited as relevant in establishing the general knowledge available in the prior art.

Ohkawa et al. teach calculating the ratio of sample values to the cut-off value to give a "cut-off index" that allows for assay results to be compared when assaying for hepatitis C virus antibody. See especially page 510, left column, last full paragraph and page 511, right column and Figure 1.

Ohnishi et al. similarly teach that in an assay for anti-HCV antibodies, levels were deemed positive when the cut-off index was greater than 1, the cut-off index being the ratio of the signal of the sample to that of a cut-off value (page 213, left column).

Hyman et al. teaches determining the signal-to-cut-off ratio (S/CO) in a method for screening for the presence of HIV-1 p24 antigen, in which values of this ratio that are greater than 1 are considered positive (Example 1, see especially at column 6, lines 5-9).

Chan et al. teach determining sample to cutoff values (S/CO) in an HCV assay, where S/CO values greater than or equal to 1.0 were considered reactive (Example 15, columns 15-16).

Yuki et al. teaches assessing samples as positive when they have a cut-off index > 1, where the cut-off value is taken as 4 times the mean negative control sample signal (abstract and page 403, left column, last paragraph).

These teachings indicate that it was routine in the art to calculate cut-off indices (also known as signal-to-cutoff ratios), where the signal from a sample is divided by a cutoff value, for the purpose of assessing whether the sample is positive or negative. Moreover, the reference teachings establish that it was known to assess whether a sample was positive when the value of the cut-off index or signal-to-cutoff ratio was greater than 1.

The prior art also recognized that cutoff values (i.e., the denominator by which the signal is divided) may be established using data from negative control samples.

For example, Lesniewski et al. discuss how cutoff levels should be selected in order to maintain acceptable assay specificity (column 12, lines 51-58). Such cutoff values should clearly separate most of the presumed "true negatives" from "true positive" specimens. The reference teaches that a general cutoff value may be calculated as about 2.1 to 8 times the negative control mean absorbance value (ibid and column 18, lines 49-56).

Kiyosawa et al. assayed for antibodies to HBc and expressed their results using the equation:

cut-off index = (net count of sample / mean of net count of negative control) x 1 / 2.1

See page 603, left column.

Yuki et al. teaches assessing samples as positive when they have a cut-off index > 1, where the cut-off value is taken as 4 times the mean negative control sample signal (abstract and page 403, left column, last paragraph).

When taken together, these various references serve to indicate that it was well known in the art of clinical diagnostics to relate assay signals to a cutoff or threshold value in order to assess the results of the assay, i.e. to decide whether a sample is positive or negative. One way in which this was often done in the prior art was to divide the assay signal by a cut-off value, known as calculating the signal-to-cutoff ratio or "cut-off index". It was further known to establish such a cutoff value by reference to a negative control. More particularly, it was known to establish cutoff values by multiplying the negative control signal by various numerical values.

As such, one of ordinary skill in the art would recognize that the equation for calculating a cutoff index (COI) in Karl et al. represented a variation on such known cutoff index calculations, where the cutoff level in Karl et al. is being obtained by multiplying the negative control signal by a value of 3.

Because the value of the selected cutoff was known to affect how the results of the assay are interpreted, i.e. whether a given sample would be classified as positive or negative, it is apparent that the cutoff value was recognized in the prior art to be a result-effective variable.

Although Karl et al. exemplify multiplying the negative control signal by 3 for those analytes such as HBsAg that were studied in the Examples, the reference clearly contemplates detection of analytes in general.

As such, absent evidence of criticality it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention out of the course of routine optimization of the cutoff value, which was known to involve multiplying the negative control signal by a numerical variable. One would be motivated to do this in order to optimize an assay for a given analyte to ensure that samples were more likely to be correctly classified as positive or negative. For

example, when using the method of Karl et al. to detect other analytes for which data is not presented in the Examples of Karl et al., it would have been obvious to apply a known technique for obtaining appropriate cutoff values, namely that of multiplying the signal for a negative control sample by a numerical variable, to the known method of detecting a plurality of analytes of Karl et al.

35. Claims 44-45, 47-48, 73, and 75-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Connor (US 5,627,026).

O'Connor et al. teach a method of detecting a plurality of analytes, namely both an antibody to and an antigen of infective agents in a single sample aliquot. See the title, abstract; and column 1, line 58 to column 4, line 41.

With respect to the recitation that the plurality of analytes are "derived from one pathogen", the Examiner notes that this recitation in the preamble does not clearly provide antecedent basis for any terms appearing in the body of the claim and is not essential to understand the limitations or terms in the claim body. Such statements merely define the context in which the invention operates and usually will not limit the scope of the claim (MPEP 2111.02 and DeGeorge v. Bernier, Fed. Cir. 1985, 226 USPQ 758, 761 n.3).

Nonetheless, O'Connor et al. teach that the infective agent may be FeLV, FIV, or HIV (column 4, lines 14-30) and assessment of simultaneous assay for antigens and antibodies associated with the same viral infection (i.e. derived from one pathogen), is clearly disclosed at lines 23-25.

The method of O'Connor et al. involves (a) providing a solid phase (solid support), which may be a non-porous material such as a microtiter well, or a glass, plastic, or latex bead (see especially column 3, lines 17-29; column 4, line 65; column 6, line 57 to column 8, line 3). An antigen capable of selectively forming an immune complex with a sample antibody (i.e., first analyte-specific receptor) is bound to the solid support at a first location, and an antibody capable of selectively forming an immune complex with a sample antigen (i.e., second analyte-specific receptor) is bound to the solid support at a separate position (see column 2, line 4 to column 3, line 7; and especially claims 1, 7, 9, and 14).

O'Connor et al. further teaches (b) contacting the sample with the solid phase and with detectable reagents. See column 3, lines 8-51, and claim 1 in particular. For example, O'Connor et al. discloses the use of a labeled antigen (i.e., third receptor) that selectively binds to a captured antibody from the sample, together with the use of a labeled antibody (i.e., another third receptor) that selectively binds to a captured antigen in the sample in a method for detecting both antibody and antigen in a single sample (claim 1). The signals generated by the detectable labels are (c) separately measured or assessed (column 5, lines 43-47 and line 65 to column 6, line 6; and the claims, e.g. claim 1, step (e)).

Regarding the step of calculating a test area-specific cut-off index, O'Connor et al. teaches measuring the signal from the signal generating group (i.e., the absorbance value at 650 nm due action of the enzyme label on TMB colorimetric substrate) for both samples and controls (positive and negative controls). This is done in order to determine whether the assay is valid: anything 3 times greater in absorbance intensity than the negative control is regarded as positive. See column 8, line 30 to column 9, line 25, and in particular at column 9, lines 17-25. This value,

the ratio of the signal from the sample well to that of the signal due to a well with negative control serum, would be considered a "test area-specific cut-off index (COI)" in the absence of a specific or limiting definition for this term. The COI taught by O'Connor et al. is 3, which is larger than 1 and therefore reads on the limitation "wherein a COI larger than 1...is indicative...".

The O'Connor et al. reference differs from the claimed invention in that the discussion of relating the A_{650} value of the sample to the negative control value is only discussed for the FIV antibody ELISA test, which only involved this one analyte and not a plurality of analytes.

However, given that O'Connor et al. focus on the determination of both antibody and antigen in a sample, it would have been obvious to one of ordinary skill to also relate the A_{650} value of the sample for antigen test areas as well. In particular, when detecting both antigen and antibody as taught by O'Connor et al., it would have been a matter of routine skill in the art to construct positive and negative controls for both antigen and antibody analytes to be detected. For example, when detecting FIV antigen in addition to FIV antibody, it would have been obvious to include a negative control for FIV antigen and to relate the signal from an FIV antibody-coated well to the signal from the negative control.

Furthermore, it would have been obvious to apply the known technique for analyzing the results from each reaction (e.g., from each sample well) in the same manner as described for the FIV antibody. One would be motivated in light of the clear teaching of O'Connor et al. that this relation of sample signal to control signal allows for the validity of the assay to be determined. As such, it would have been obvious to calculate a COI for antibody as well as for antigen in order to determine whether the sample was in fact positive for the presence of each of these analytes.

With respect to claim 45, O'Connor et al. teach detection of both HIV antigen and anti-HIV antibody (column 4, lines 23-25). Hepatitis B (i.e., HBV) antigen is also contemplated (see column 4, lines 6 and 17 and claim 13).

With respect to claim 47, O'Connor et al. teach controls, e.g. control wells coated with receptor and to which positive or negative control sample is added (column 8, lines 59-65). Alternatively, a negative control can be performed with a non-specific antibody (column 5, lines 48-65). This is done to control for nonspecific reactions, i.e. "interferences".

With respect to claim 48, O'Connor et al. teaches detection reagents comprising a third receptor specific for the analyte (e.g., antibody or antigen specific for antigen or antibody, respectively) bound directly to a signal-generating group (enzyme). See column 3, lines 8-51; column 7, lines 8-30 and 47-51; column 8, lines 50-56).

With respect to claim 76, O'Connor et al. teaches that the detectable labels may be enzyme labels (column 3, lines 47-51).

With respect to claim 75, O'Connor et al. teaches detecting HIV p24 antigen and anti-HIV antibody (column 4, lines 23-30).

With respect to claim 77, O'Connor et al. teaches detection of Hepatitis B (i.e., HBV) antigen (see column 4, line 6) but fails to specifically teach detection of more than one analyte "derived from" HBV. However, as discussed above this terminology appears only in the preamble of the claim and does not clearly further limit the claim scope, such that the reference would read on the claim. Nonetheless, O'Connor et al. teach simultaneous assaying for antigens and antibodies associated with the same viral infection (column 4, lines 23-25). Although HIV and not HBV is exemplified in this context the focus, it would have been obvious to one of

ordinary skill in the art to select HBV from the finite number of viruses disclosed in the reference and to detect both HBV antigen in addition to anti-HBV antibody.

36. Claim 46 is rejected under 35 U.S.C. 103(a) as being unpatentable over O'Connor et al. in view of Ekins (US 5,837,551, of record).

O'Connor et al. is as discussed above, which teaches test areas on non-porous solid supports such as microtiter plates. However, the reference fails to specifically teach that the test areas have diameters of 0.01 – 1 mm.

Ekins teaches forming arrays of "microspots" in which binding agents (i.e., receptors) are immobilized into defined, spatially separated test zones (i.e., "test areas") on a solid support (column 2 line 35 to column 4 line 41). The microspots preferably have an area of less than 1000 square microns, e.g. 0.1 square mm, and can be for example of diameter 80 microns or 0.08 mm (column 3, lines 34-63; column 4, line 2). By providing such microspot arrays, a plurality of analytes may be simultaneously determined (column 3, lines 40-47). The microspots can be formed on a microtiter plate, i.e. non-porous support (column 7, lines 33-40). Binding of analytes to the binding agents immobilized in each microspot is then assessed using a detection agent capable of binding to the analyte and including a marker, e.g. an enzyme or fluorescent marker (column 3, lines 10-33).

Such miniaturized test zones contain small amounts of binding agent, allowing binding assays to be conducted with rapid kinetics to minimize the time needed to complete the assay (column 6, lines 4-8). In addition, less of the binding agent is necessary, diffusional constraints are reduced and assay sensitivity is also improved (column 6, lines 9-32).

Therefore, it would have been obvious to one of ordinary skill in the art to modify the method of O'Connor et al. by depositing the first and second receptors into small test zones or "microspots" (e.g., of diameter 0.08 mm on a microtiter plate) as taught by Ekins et al. because detection of antibody and antigen could be conducted more rapidly and with greater sensitivity and would also require less of the capture reagents to be consumed.

When performing the method of O'Connor et al. using microspots in this manner, it would have been further obvious to employ the detection scheme taught by Ekins to be suitable for the microspot arrays, namely by using a detection agent capable of binding to analyte (i.e., third receptor) and including a marker capable of producing the signal for the assay.

37. Claims 78-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Connor in view of Betts Carpenter ("Enzyme-Linked Immunoassays" In: Manual of Clinical Laboratory Immunology, Noel R. Rose et al. (Eds), ASM Press, Washington, DC (1997) Fifth Edition, pages 20-29, Ohkawa et al., Ohnishi et al., Hyman et al., Chan et al., Lesniewski et al., Kiyosawa et al., and Yuki et al.

O'Connor et al. is as discussed above, which teaches a method substantially as claimed in which a cut-off index is calculated by relating the sample signal to the signal from a negative control. In particular, O'Connor et al. teach that an absorbance signal greater than 3 times the mean negative control absorbance indicates that the sample is positive (column 9, lines 17-25).

However, O'Connor et al. differs from the claimed invention in that it fails to specifically teach first subtracting "background $_{sample}$" from the numerator in the above equation. The

reference also fails to specifically teach multiplying "background $_{\text{negative control}}$" by a number *n* between 2 and 100, or in particular between 2 and 10, or in particular by 2.

Regarding subtraction of "background $_{\text{sample}}$", it was known in the art to subtract background measurements in order to obtain a net signal. For example, Betts Carpenter teaches that when detecting colorimetric substrates by spectrophotometry in ELISA assays, OD measurements (i.e., the assay signals) can be blanked on air, or alternatively on a well containing either substrate, substrate-Ab conjugate alone, or a negative serum in an uncoated well (see especially page 25, "Substrates").

Therefore, although O'Connor et al. is silent as to whether the absorbance signal taken represented a signal from which background was subtracted, it would have been obvious to subtract background from the raw absorbance signal in accordance with routine laboratory procedures. For example, it would have been obvious to blank the spectrophotometer on air or on a well containing colorimetric substrate in the method of O'Connor et al., which would be tantamount to subtracting a background measurement for the sample to produce a corrected signal. Blanking a spectrophotometer, as taught by Betts Carpenter, would be at once envisaged by a person of ordinary skill in the art familiar with such equipment. One would be motivated to combine the reference teachings in this manner because Betts Carpenter relates to laboratory procedures for performing ELISA assays, which is the method used in O'Connor et al. as discussed above.

Regarding the multiplier *n* in the denominator of the equation recited in claim 78, O'Connor et al. analyzed the results of the FIV antibody assay by assessing whether the signal-to-negative control ratio was greater than 3. It would also be a simple matter to determine this by

simply multiplying the negative control absorbance by 3, and then determining whether the signal value was greater than this value, i.e. whether $Signal_{sample}$/ $background_{negative\ control}$ is greater than 1. In such a case, the value 3 as taught by O'Connor would be equivalent to the instantly claimed *n*. As such, it would also have been obvious to arrive at the claimed invention of claims 78-79 by relying on simple algebraic calculations in the course of assessing whether the signal-to-negative control ratio was greater than 3 as directed by O'Connor et al.

This feature of dividing by a multiplier of the negative control value is also found obvious in view of the teachings of Ohkawa et al., Ohnishi et al., Hyman et al., Chan et al., Lesniewski et al., Kiyosawa et al., and Yuki et al. As discussed in detail above, these references establish that it was known in the art to calculate signal to cutoff ratios (also known as "cut-off indices"), and further that the value of the cutoff may be selected based on data obtained from a negative control.

When taken together, these various references serve to indicate that it was well known in the art of clinical diagnostics to relate signals from an assay to signals that of a cutoff or threshold value in order to assess the results of the assay, i.e. to whether a sample is positive or negative. One way in which this was often done in the prior art was to divide the assay signal by a cut-off value, known as calculating the signal-to-cutoff ratio or "cut-off index". It was further known to establish a cutoff value using a negative control. Specifically, it was known to establish cutoff values by multiplying the negative control signal by various numerical values, or alternatively by adding various numerical values to the negative control signal.

Furthermore, as discussed above the value of the selected cutoff was known to be a result-effective variable that affects how the results of the assay are interpreted, i.e. whether a given sample would be classified as positive or negative.

As such, absent evidence of criticality it would have been obvious to one of ordinary skill in the art to modify the teachings of O'Connor et al. and Betts Carpenter, in which a blanked signal is divided simply by the straight, unadjusted negative control absorbance, by first multiplying the negative control signal by a numerical value prior to determining the signal-to-control ratio cut-off index). In particular, in light of the general knowledge in the prior art (as taught by Ohkawa et al., Ohnishi et al., Hyman et al., Chan et al., Lesniewski et al., Kiyosawa et al., and Yuki et al.), it would have been obvious to optimize the value of the parameter to which the signal from the sample is compared in this manner out of the course of routine optimization in order to ensure that samples were more likely to be correctly classified as positive or negative. For example, when using the method of O'Connor et al. and Betts Carpenter to detect other analytes besides the exemplified FIV antibody, it would have been obvious to apply a known technique for obtaining appropriate cutoff values, namely that of multiplying the signal for a negative control sample by a numerical value, and then dividing the signal by this product, to the known method of detecting a plurality of analytes of O'Connor et al. in order to optimize the assay. It would have been further obvious to arrive at the claimed value of n (e.g., n=2) out of the course of routine optimization, given that the cut-off value (a component of which is n) was recognized in the art as a result-effective variable.

Double Patenting

38. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

39. Claims 44-48, 73, and 75-77 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 6,815,217 in view of Schonbrunner (GB 2 313 666 A, of record).

U.S. Patent No. 6,815,217 claims an assay device and method for determining an analyte, in which a solid phase is provided that contains a receptor that includes a binding site for specifically binding with the analyte (i.e., analyte-specific receptor) in a defined region of the support (see especially claim 19). The analyte may be HIV antibodies, HBs antigens, and HBc antibodies (claims 18 and 30). The solid phase may also include a control area (see claim 19). The solid phase may be provided together with a third receptor capable of binding to the analyte, which receptor may include a signal generating group (see claims 19 and 34).

U.S. Patent No. 6,815,217 further recites that the amount of analyte can be quantitatively determined by correcting the value of the signal generated by the marker in the test area to the signal generated by the marker in a control area (claims 19-22). This may involve subtraction of these values (claim 22), i.e. a calculation. In the absence of a specific or limiting definition of the term "cut-off index", the value obtained by this calculation may be considered such an index.

Although US 6,815,217 fails to specifically recite that a COI larger than 1 indicates the presence of a specific analyte, when the claims are given their broadest reasonable interpretation such a statement may be interpreted as merely a characterization or conclusion of the method steps earlier recited. For example, such a statement could be reasonably interpreted as simply reflecting fundamental physiological relationships of the analytes that are determined, which would necessarily apply in the assay method. The recited "wherein" phrase does not clearly call for an active method steps to be performed or designate structural limitations. For all of these reasons, the calculation performed in US 6,815,217 reads on that claimed instantly.

Regarding the claimed "plurality of analytes" that are detected, US 6,815,217 does recite that the solid support may also comprise a second test area in a separate defined region that comprises a second receptor that is specific for a second analyte (see claim 17 in particular). However, US 6,815,217 differs from the instant claims because there is no explicit recitation that the method detects both the first and second analyte, i.e., a "plurality of analytes derived from one pathogen". In addition, US 6,815,217 does not specifically recite that the support is "non-porous".

However, it would have been obvious to one of ordinary skill in the art to envisage that a solid support containing first and second receptors specific for first and second analytes was

intended for the purpose of detecting both first and second analytes. Furthermore, the analytes detected in US 6,815,217 may be for example antibodies or antigens, in particular HIV antibodies or HBs (hepatitis B) antigens or HBc antibodies (see claims 18 and 30).

As such, it would have been obvious to one of ordinary skill in the art to perform the method of US 6,815,217 using a solid support having receptors for both HBs antigens and HBc antibodies as the analytes, given that these two analytes are clearly recited as part of a finite list of preferred analytes to be detected. One would be motivated to arrive at such a combination and would have a reasonable expectation of success in so doing since US 6,815,217 recites a device comprising multiple test areas containing multiple receptors for specifically binding to multiple analytes. The use of such a multiply-coated device for the purpose of detecting multiple analytes would be at once envisaged by the person of ordinary skill in the art.

In addition, Schonbrunner et al. teaches that the detection of both HIV antigen and antibody in a sample allows HIV to be specifically detected at a very early stage of the infection (pages 2-3 and 6-7). Schonbrunner et al. also teaches that antigens or antibodies can be attached to a support in order to detect HIV antibody and antigen, respectively (page 20). The solid support is not critical and can be any material which is insoluble or can be made insoluble, e.g. glass, plastic, metal, or a microtiter well (page 20, lines 9-14).

Therefore, it would also have been obvious to one of ordinary skill in the art to employ first and second receptors for HIV antigen and antibody, respectively, in the method of U.S. 6,815,217 B2 in order to detect HIV infection earlier in light of the teachings of Schonbrunner. In particular, would be modify the teachings of US 6,815,217, in which HIV antibody alone may

be detected as the analyte, by detecting both HIV antibody and HIV antigen so as to allow for HIV infection to be detected and in particular at an early stage of infection.

It is noted that the method and device of U.S. 6,815,217 B2 employs separate test and control areas that are separately measured for signal (see especially steps (c) and (d) of claim 19). Therefore, when performing the method of U.S. 6,815,217 B2 and Schonbrunner et al. to detect HIV antibody and antigen, it would have been further obvious to employ this known technique in order separately detect signals in the test areas for each of these two analytes in the same manner. Likewise, it would have been obvious to calculate subtract the signal from the control area from the signal for each analyte (i.e., calculate a test area-specific COI for each test area) when detecting a plurality of analytes according to the method of U.S. 6,815,217 B2 and Schonbrunner et al. so that the amount of each analyte could be quantitatively determined in the same manner as for a single analyte.

Furthermore, although US 6,815,217 does not specifically recite that the solid phase comprises a "non-porous" support, it would have been obvious to one skilled in the art to employ the specification as a dictionary in order to interpret the meaning of the term "solid phase support" in carrying out the claimed invention. In introducing the solid phase support, the specification of US 6,815,217 at column 2, lines 29-32 states that the support is preferably non-porous. In addition, in light of the teachings of Schonbrunner et al. which indicate that the material for a solid support on which capture reagents are attached can be such non-porous supports as plastic or glass, it would have been further obvious to one of ordinary skill in the art to select such a known material for its known purpose with a reasonable expectation of success.

With respect to claim 46, US 6,815,217 recites that the solid support test area and control area may each have a diameter of 10 microns - 1 cm (claim 14), i.e. 0.01 mm - 10 mm. Because the claimed range of 0.01 - 1 mm lies inside the range recited in US 6,815,217, a prima facie case of obviousness exists (see MPEP 2144.05). Therefore, it would have been obvious to one of ordinary skill in the art to arrive at the claimed range in the course of routine optimization, out of the normal desire of artisans to improve on what is already known.

With respect to claim 47, US 6,815,217 recites that the solid support may include a control area for binding to interfering substances (claims 19 and 34, steps (a)(ii) and also claims 1-8 and 27-28).

With respect to claim 48, US 6,815,217 recites a marker that is capable of generating a detectable signal and binding with the analyte (i.e., third receptor). See claim 34 of US 6,815,217.

With respect to claim 75, US 6,815,217 recites HIV antigens as possible analytes but does not specify specific HIV antigens or antibodies. Schonbrunner et al. further teaches that simultaneous detection of the presence of both antigen and antibody analytes of HIV in a sample provides a possibility for specifically detecting the presence of HIV in a sample at a very early stage of infection. See pages 5-6, especially at the paragraph bridging the pages and at page 6, lines 26-29. The HIV-1 antigen p24 is taught, although other HIV gag antigens are contemplated (page 6, lines 29-32 and page 25). Detection of antibodies to HIV gp41 is also taught (page 26, lines 4-9).

Therefore, it would have been further obvious to one of ordinary skill in the art to employ the method of US 6,815,217 in order to detect both HIV antigen (e.g., p24) in addition to the

anti-HIV antibodies recited in US 6,815,217 because this would allow for HIV to be detected at an earlier stage of infection, thereby closing the diagnostic window. It would have been further obvious to detect those anti-HIV antibodies that target HIV gp41 as taught by Schonbrunner

With respect to claim 76, US 6,815,217 recites a marker capable of generating a detectable signal but does not specifically recite those types of markers recited. Schonbrunner teaches markers or labels that are used to generate a measurable signal (page 23, lines 4-34). In particular, Schonbrunner et al. teach chemiluminescent compounds, enzymes, fluorescent compounds and others. Therefore, it would have been further obvious to employ a chemiluminescent group or an enzyme as taught by Schonbrunner as the marker in the method of US 6,815,217 since these were known to be suitable for the purpose of generating a measurable signal, which is the same purpose for which the markers in US 6,815,217 are employed.

With respect to claim 77, US 6,815,217 recites detection of HIV antibodies but does not specify the type of HIV. Schonbrunner teaches that HIV-1, HIV-2, and HIV-3 variants were known, and that the detection of a variety of HIV's can be achieved by using the appropriate capture reagents (pages 8-9, 15, and 33). Given that a finite number of types of HIV were known in the art as indicated by Schonbrunner, it would have been obvious to detect analytes "derived from" HIV-1, HIV-2, and/or HIV-3 because these were the types of HIV known in the art. Therefore, one would be motivated to detect analytes associated with any of these known strains in order to assess HIV infection.

40. Claims 78-80 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 6,815,217 in view of

Schonbrunner (GB 2 313 666 A) as applied to claim 44 above, and further in view of Ohkawa et al., Ohnishi et al., Hyman et al., Chan et al., Lesniewski et al., Kiyosawa et al., and Yuki et al.

U.S. Patent No. 6,815,217 is as discussed above, which recites subtracting signal from a control area from signal in the test area, i.e. "$Signal_{sample}$" - "background $_{sample}$" (see especially claims 19 and 22). However, U.S. Patent No. 6,815,217 fails to specifically recite dividing the resulting value by n x background $_{negative\ control}$, where n is between 2 and 100, between 2 and 10, or is 2.

The teachings of Ohkawa et al., Ohnishi et al., Hyman et al., Chan et al., Lesniewski et al., Kiyosawa et al., and Yuki et al. are discussed in detail above. When taken together, these various references serve to indicate that it was well known in the art of clinical diagnostics to relate signals from an assay to cutoff or threshold values in order to assess the results of the assay, i.e. to conclude whether a sample is positive or negative. One way in which this was often done in the prior art was to divide the assay signal by a cut-off value, known as calculating the signal-to-cutoff ratio or “cut-off index”. It was further known to establish a cutoff value using a negative control. Specifically, it was known to establish cutoff values by multiplying the negative control signal by various numerical values, or alternatively by adding various numerical values to the negative control signal.

Furthermore, as discussed above the value of the selected cutoff was known to be a result-effective variable that affects how the results of the assay are interpreted, i.e. whether a given sample would be classified as positive or negative.

As such, absent evidence of criticality it would have been obvious to one of ordinary skill in the art to divide the net signal ("$Signal_{sample}$" - "background $_{sample}$") taught by U.S. Patent No.

6,815,217 by a cut-off value obtained by multiplying the signal from a negative control by a numerical value. One of ordinary skill in the art would have been motivated to in order to assess the results of the assay and to determine whether a given sample was positive or negative. It would have been further obvious to arrive at the claimed value of *n* (e.g., 2) out of the course of routine optimization, given that the cut-off value (a component of which is n) was recognized in the art as a result-effective variable.

Response to Arguments

41. With respect to the rejections of claims 44-48 and 73 on the grounds of nonstatutory obviousness-type double patenting over US 6,815,217, Applicant's argues that the claims are patentably distinct but apparently simply restates claim language verbatim and does not point out how the language of the instant claims renders them patentably distinct. Such remarks do not comply with the requirements of 37 CFR 1.111 because Applicant has not specifically pointed out how the language of the newly presented claims patentably distinguishes them from US 6,815,217.

42. The remainder of Applicant's arguments are acknowledged but are moot in light of the new grounds of rejection as set forth above.

Conclusion

43. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

44. Urnovitz et al. (US 5,447,837) teaches solid support-based methods for detection of antibodies and antigens, such as those associated with HIV or HCV.

45. Stewart et al. (US 4,983,529), Nishiguchi et al. ("Detection of hepatitis C virus antibodies and hepatitis C virus RNA in patients with alcoholic liver disease" Hepatology. 1991 Dec;14(6):985-9), and Luciw et al. (US 7,205,101 B1) are also cited as relevant to the claimed step of calculating a COI.

Stewart et al. teaches dividing a sample signal by a cutoff value and characterizing samples as positive when the result is greater than or equal to 1 (column 4, lines 10-14).

Nishiguchi et al. teaches expressing results of a diagnostic ELISA for HCV in terms of a COI calculated as the ratio of the OD of the sample divided by the mean OD of negative control samples plus 0.4 OD units (see especially Figure 1 and legend and page 986, right column, "Results".

Luciw et al. disclose setting cut-off levels for the analytes env-2 and env-5b at 5 times the average signal of seronegative specimens, i.e. negative controls (column 68, lines 49-58).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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